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Editorial

BE PROUD YOU ARE A PHYSIOLOGIST

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— The study of physiology traces its roots back to ancient India and Egypt. As a medical discipline, it goes back at least as far as the time of Hippocrates, the famous "father of medicine" – around 420 BC **(Fox, 2020).** Hippocrates coined the theory of the four humors, stating that the body contains four distinct bodily fluids: black bile, phlegm, blood, and yellow bile. Any disturbance in their ratios, as the theory goes, causes ill health. Claudius Galenus (c.130-200 AD), also known as Galen, modified Hippocrates' theory and was the first to use experimentation to derive information about the systems of the body. He is widely referred to as the founder of experimental physiology **(Goodacre, 2020).** It was Jean Fernel (1497-1558), a French physician, who first introduced the term "physiology," from Ancient Greek, meaning "study of nature, origins." Fernel was also the first to describe the spinal canal **(Ambrose, 2021).** Another leap forward in physiological knowledge came with the publication of William Harvey's book titled An Anatomical Dissertation Upon the Movement of the Heart and Blood in Animals in 1628. Harvey was the first to describe systemic circulation and blood's journey through the brain and body, propelled by the heart **(Aird, 2011).** In 1838, a shift in thought occurred when the cell theory of Matthias Schleiden and Theodor Schwann arrived on the scene. From here on in, the field of physiology opened up, and progress was made quickly. **Georg Prochaska** (1749-1820), Prochaska was a pioneer in the field of neurophysiology, being remembered for developing a comprehensive theory of reflex action. Joseph Lister, 1858 – initially studied coagulation and inflammation following injury, he went on to discover and utilize lifesaving antiseptics. Ivan Pavlov, 1891 – conditioned physiological responses in dogs **(Rossiianov and Seay, 2017).**

Physiology as the Underpinning of Medicine

Physiology has a long history of two-way interactions with clinical medicine **(Joyner, 2011).** Physiology as an experimental discipline emerged in North America during the 1820s as Beaumont studied the gastric secretions of the French-Canadian trapper Alexis St. Marin who had a posttraumatic fistula that permitted easy access to the gastric contents **(Rutkow. 2010).**

What follows are a few thoughts on why physiology matters more than ever in medicine.

The parallels between classic integrative physiology experiments and what happens to patients during anesthesia, in the intensive care unit or in the cardiac catheterization laboratory, seem obvious to even the most casual observer**(Austin et al, 2010).** Additionally, many diagnostic tests like the simple measurement of electrolytes and plasma creatinine are based on the idea that, by simply measuring a few key physiological markers, it is possible to gain insight into the pathophysiology of an individual patient. Physiology is also at the heart of such common tests as the electrocardiogram, simple measurements of blood pressure, exercise based "stress tests," renal clearance measurements, GI motility studies, pulmonary function, and a host of others. For each of the examples cited above (and there are many more), there is a clear narrative that shows how physiology as an experimental discipline has been involved in both an intellectual and applied serve and volley with clinical medicine**(Joyner, 2011)**.

There are multiple examples of transformational therapies based on physiological insights. Here are a few:

1) One of the most common causes of death in the world is diarrheal illness in infants and children. This disease can be treated and the victims rescued from certain death with simple oral rehydration solutions based on the fundamental principles of physiological regulation of fluid and electrolyte balance along with GI and renal physiology **(Beekman et al, 2020).**
2) Premature birth was once associated with either certain death or an incredible burden of comorbidities in the survivors. The fundamental issue driving many of these problems was the immature lung and a host of complications associated with maintaining gas exchange in premature infants and oxygen toxicity **(Bunton , 2011).** These problems have largely been solved by a multidisciplinary approach, all based on better physiological management of these tiny humans, along with the development of surfactant therapy to improve ventilation and gas exchange and allow much shorter periods of respiratory support at vastly reduced ventilator settings. Anyone who practiced medicine or nursing in the 1980s and worked with survivors of neonatal ICUs still has a hard time believing just how intact premature babies born in the postsurfactant era are as infants, toddlers, and children **(Joyner, 2011)**.
3) Treatment of coronary artery disease: the per capita age-specific death rates for coronary artery disease have declined by 60–70% since the 1960s. Much

of this decline has been due to the therapeutic implications of the simple understanding of the balance between oxygen supply and oxygen demand by the heart. This simple relationship has led to highly effective mechanical therapy (surgery, angioplasty, stents), drug therapy (e.g., statins, β-blockers, and other antihypertensives), and other short- and long-term interventions to either improve the balance between supply and demand or prevent it from deteriorating in the first place. The most notable recent examples in this area include incorporation of ideas from the EFRF/NO era into the vulnerable plaque model and the acute coronary syndrome and the effective use of anticoagulants and thrombolytic agents **(Cheng et al. 2015).**

4) Use of β-blockers and vasodilator therapy in the treatment of congestive heart failure (CHF). At one time, it was thought that β-blockers would contribute to a worsening of cardiac function in CHF because high levels of reflex sympathetic activity were required to maintain arterial pressure in the face of reduced cardiac pumping capacity. However, via multidisciplinary approaches, it was shown that the high levels of sympathetic activation associated with CHF were in fact part of the problem, and drug regimens designed to blunt the impact of the sympathetic activation associated with CHF have been life extending for many patients. Again, physiological insights and explanations for this problem were key to the development of new therapeutic approaches **(Clements and Averg, 2018).**
5) A similar story can be told about the Adult Respiratory Distress Syndrome (ARDS). For many years, the goal in critically ill patients requiring mechanical ventilation was to keep blood gases and pH as near normal as possible. This frequently required high tidal volumes and the associated high pulmonary pressures, which resulted in barotrauma to the lung and frequently made matters worse. In this context, more modest levels of ventilation with less than perfect blood gas values have been shown to improve outcomes in ARDS patients, and the explanations for these positive outcomes is physiologica **(Chong et al. 2021).**
6) Exercise training is a powerful preventive intervention and treatment for Type 2 diabetes. The improved glucose control evoked by exercise is multi-factorial but has led to a number of insights about insulin-independent glucose transport in muscle and a variety of observations about the physiology of whole body glucose metabolism **(Meza, 2018).**
7) A number of physiologically based insights and therapeutic approaches in fact made vast and significant inroads into clinical medicine. Perhaps the most notable example of the continued success of physiology as the backbone of medicine is the discovery of endothelial-derived relaxing factor (EDRF) and the subsequent identification of NO as the main EDRF. The fundamental discovery underpinning all of this was made in an organ bath using isolated blood vessel preparations. The observations that flowed from the EDRF story led to an explosion of new knowledge, including identification of a new family of gas-based biological signaling pathways,

new ideas about the role of the vascular endothelium in health and disease, new pathophysiological explanations for a host of syndromes, and new treatments for a number of diseases including erectile dysfunction and pulmonary hypertension **(Paul et al. 2021)**.

1. **What physiologists have provided to serve medicine and save humanity and they deserved a Nobel Prize (Rydén and Lindsten, 2021).**

— **August Krogh, (1910):** for discovering how blood flow is regulated in capillaries.

— **William Einthoven (1924):** for the discovery of the mechanism of the electrocardiogram").

— **Charles Scott Sherrington (1932)**: for his work on the functions of neurons and explanation of synaptic communication between neurons helped shape our understanding of the central nervous system.

— **Joseph Erlanger and Herbert Spencer Gasser(1944):** for their discoveries relating to the highly differentiated functions of single nerve fibers and types of nerve fibers(A,B,C),propagation of action potential and registration of electrical changes on the nerves."

— **Andrew Huxley and Alan Hodgkin (1952):** For the discovery of the ionic mechanism by which nerve impulses are transmitted.

— **Andrew Huxley and Hugh Huxley (1954):** Made advances in the study of muscles with the discovery of sliding filaments in skeletal muscle.

— **John Carew Eccles, Alan Lloyd Hodgkin and Andrew Fielding Huxley (1963):** For their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane.“

— **Alfred G. Gilman and Martin Rodbell (1994):** For their discovery of “G-proteins and the role of these proteins in signal transduction in cells”

— **Günter Blobel (1999):** For the discovery that proteins have intrinsic signals that govern their transport and localization in the cell.

— **Arvid Carlsson, Paul Greengard and Eric R. Kandel (2000):** For their discoveries concerning signal transduction in the nervous system.

— **Leland H. Hartwell, Tim Hunt and Sir Paul M. Nurse (2001):** For their discoveries of key regulators of the cell cycle.

— **Sydney Brenner, H. Robert Horvitz and John E. Sulston (2002):** For their discoveries concerning genetic regulation of organ development and programmed cell death.

— **Richard Axel and Linda B. Buck (2004):** For their discoveries of odorant receptors and the organization of the olfactory system.

— **Jeffrey C. Hall, Michael Rosbash, Michael W. Young (2017):** For their Discoveries of Molecular Mechanisms Controlling the Circadian Rhythm.

— **William G. Kaelin Jr, Sir Peter J. Ratcliffe and Gregg L. Semenza (2019):** For their discoveries of how cells sense and adapt to oxygen availability."

— **David Julius and Ardem Patapoutian (2021):** For their discoveries of receptors for temperature and touch **(Logan, 2021).**.

- **Julius and Pataboutian (2021)** Patapoutian focused their work on the field of somatosensation, that is the ability of specialized organs such as eyes, ears and skin to see, hear and feel.
- This really unlocks one of the secrets of nature, It's actually something that is crucial for our survival, so it's a very important and profound discovery.
- Julius worked on this puzzle with the help of the molecule capsaicin, which is responsible for the burning sensation that chili peppers deliver. Screening a library of genes from sensory neurons to discover proteins that were sensitive to capsaicin led his team to one specific ion channel, TRPV1, that reacts to both capsaicin and pain-inducing heat
- Patapoutian found separate pressure-sensitive sensors in cells that respond to mechanical stimulation.
- Just a few years later Julius and Patapoutian independently discovered the cold-sensing receptor TRPM8, which is activated by menthol
- Both researchers have continued to study these TRP channels, but Patapoutian also focused on ion channels that detect mechanical force. The channels his team discovered, called PIEZO1 and PIEZO2, change their shape when the cell membranes they sit within bend in response to a touch or a poke. The change in shape opens the channels, allowing ions to flow across the membrane and generate a signal.
- One of the big reasons why this particular prize was highly appropriate, is that not only did these two labs discover these proteins, but they have gone to great lengths to explain how they work at an atomic level, the fact that there may be implications for human disease and the fact that new therapies for pain have been very hard to come by, I think that just add to the impact of this work."
- Julius and Patapoutian's work "have launched pain and sensory research into the molecular stratosphere," and today entire fields of research have been built on the work of the two researchers. The next step, she says, is to figure out how to target ion channels including those identified by Julius and Patapoutian to alleviate different forms of pain **(Logan, 2021).**

"The Death of Physiology" Is this idea scientifically acceptable?

- The successes noted above are of course very gratifying and give physiologists a chance to say I told you so! However, can new clinical successes dependent on physiology emerge in the future? The short answer is that only time can tell because the nature of medical progress is nonlinear and sometimes counter-intuitive. The discovery of EDRF/NO is an example of serendipity, and the emergence of Viagra (which was initially developed as a potential therapy for angina) shows the nonlinear nature of progress. β-Blockers for CHF and kinder, gentler ventilator support in ARDS seemed counter intuitive when first proposed **(Joyner, 2011)**. In this context, a couple of areas seem ripe for improvement by "physiological thinking." Here are a two.

a) Alzheimer's disease (AD) research is focused largely on amyloid accumulation in the brain. However, the epidemiological risk factors for mild cognitive impairment and AD are essentially the same as well-known cardiovascular risk factors such as hypertension, diabetes, and inactivity. In this context, what is the role of the cerebral circulation, especially the microcirculation in AD? Perhaps AD is merely "brain failure," and for many other forms of organ failure microvascular dysfunction is a major contributor. Do physiologists have insights that can help find answers and hopefully interventions in AD (**Ferretti et al 2020).**
b) Aging is associated with frailty, and frailty is associated with poor outcomes in older people. A key contributor to frailty is muscle loss (sarcopenia). The best current preventive strategies for frailty center around exercise, and the search is already on to understand how aging muscle does or does not respond to exercise and how these responses change with aging **(Ma et al, 2018).**

- In addition to these examples, the world-wide obesity epidemic clearly has a number of potential physiological explanations that intersect with behavioral science when humans live in low physical activity, high-calorie environments. Finally, physiology is informed by concepts like regulated systems, feedback control, and redundancy that operate to keep critical homeostatic variables in normal range. Some of these mechanisms, like baroreceptor resetting, can be hijacked in disease and actually begin to operate in a way that maintains the pathophysiological state in conditions like resistant hypertension. This makes it even more likely that there will not be silver bullets for complex diseases and again highlights the need for more and not less physiological thinking **(Joyner, 2011)**..

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